patent and application of the term "Fas ligand" is contrary to the accepted and universally applied meaning of the term in the field of the invention. "Fas ligand" is recognized in the field of the invention as being a specific protein and MORT-1 would not be considered "Fas ligand." Attached hereto as Exhibit A is a printout from the "Online Mendelian Inheritance in Man" ("OMIM") from the Johns Hopkins University. As indicated from the OMIM data printout, "Fas ligand" is the name of a specific protein and not a term referring generally to every possible ligand that binds to Fas. As such, MORT-1 is not "Fas ligand" and one skilled in the art would never interpret it as such. The present invention is, therefore, not anticipated by the '327 patent and withdrawal of the rejection is respectfully requested.

Rejections under 35 U.S.C. §103

The Examiner further maintains the rejection of the claims as noted in the final office action as being obvious under 35 U.S.C. § 103 over: a) Keana et al., U.S. Pat. No. 6,184,210;

b) Hughes & Crispe combined with Holoshitz et al., U.S. Pat. No. 6,098,631 and D'Souza;

c) Nagata et al., U.S. Pat. No. 6,348,334 combined with the '631 patent and Queen et al., U.S. Pat. No. 6,046,310;

d) Lynch et al., U.S. Pat. No. 5,830,469 combined with D'Souza;

e) the '469 patent combined with Aoyagi, EP 0 285,883; or

f) the '210 patent or Hughes & Crispe combined with the '631 patent and D'Souza and further combined with the '334 patent.

In the Advisory Action and in response to Applicant's remarks of December 31, 2002 regarding the above rejections, the Examiner asserts that Applicant's interpretation of Elliot et al. is incorrect. The Examiner interprets the discussion on page 1609, right column of Elliot et al. (first incomplete paragraph) as teaching that more than one mechanism may be involved in MS and explaining why FAS-deficient mice still suffer EAE, rather than teaching away from the involvement of FAS per se with MS.

The Examiner further disagrees with the argued interpretation of D'Souza. The Examiner reiterates that D'Souza teaches that Fas is involved in MS, but not apoptosis. Thus, inhibiting FAS-mediated pathways may be effective against MS, although not through the inhibition of apoptosis.

The following supplemental remarks address the comments of the Examiner in the Advisory Action regarding Elliot et al. and D'Souza. As noted above, in the Advisory Action the Examiner disagrees with Applicant's assertion that results of D'Souza suggest that the Fas-Fas ligand pathway is not involved with MS and disagrees with Applicant's interpretation of Elliot et al.

Applicants believe that the discussions thus far regarding the involvement of the Fas-Fas ligand pathway with MS may have oversimplified that involvement, leading to confusion in the

understanding of the invention and the communication between Applicants and the Examiner. Thus far the involvement of the Fas-Fas ligand pathway in relation to MS has been discussed as a single matter. In fact, there are two mechanisms by which the Fas-Fas ligand pathway is involved with the pathology of MS.

With the first mechanism of "involvement" of the Fas-Fas ligand pathway in MS, inhibiting the activity of the Fas-Fas ligand system to thereby inhibit apoptosis may be useful for reducing immunological functions which cause MS-associated conditions. On the other hand, a second mechanism of involvement of the Fas-Fas ligand system with MS exists in which the Fas-Fas ligand-induced apoptosis is used as a means for eliminating unnecessary cells from a living body. These two types of mechanisms are in complete opposite with each other but described in the same terms of involving "the relation between MS and Fas-Fas ligand pathway" or by indicating that MS is involved in Fas-Fas ligand pathway. Attached hereto as Exhibit B is a depiction of the two mechanisms of involvement of the Fas-Fas ligand pathway in MS.

The first "involvement" of the Fas-Fas ligand system described above is disclosed in D'Souza with the indication of "oligodendrocyte destruction(demyelination) in MS due to apoptosis of Fas-FasL pathway". D'Souza shows Fas is expressed in a high ratio in oligodendrocytse. But "apoptosis by Fas" in the oligodendrocyte has not yet been shown. Thus, the reference

only teaches that the Fas-Fas ligand pathway may have some connection with oligodendrocyte destruction in MS, but the relation between Fas-Fas ligand pathway and MS has been not proven only speculated.

On the other hand, Elliot verifies that EAE appears in Fas deficient mice. The fact that EAE appears in Fas deficient mice is inconsistent with the suggestion of D'Souza that the Fas-Fas ligand pathway may have a connection in any way with oligodendrocyte destruction in MS. Thus, in comparing the disclosures in D'Souza with Elliot it is seen that in that state of the art there were inconsistent data about whether the oligodendrocyte destruction in MS is due to apoptosis induced by the Fas-Fas ligand pathway or not. Whether the oligodendrocyte destruction in MS is due to apoptosis of Fas-FasL pathway or not was very controversial. It is not appropriate to consider only data in favor of the Examiner's position and not consider the overall state of the art, including equally accepted data that is inconsistent with suggesting the invention.

As discussed above, the second mechanism of "involvement" of the Fas-Fas ligand pathway with MS is based on the elimination of the auto reactive T cells in body due to the Fas-Fas ligand pathway. The onset of MS occurs when auto reactive T cells react with the "self" tissue. As understood in immunology textbooks, under normal conditions, such auto reactive T cells are eliminated by clonal deletion through apoptosis. When the

apoptosis mechanism does not occur appropriately, MS can occur. Whether the normal clonal deletion is due to the Fas-Fas ligand pathway is the second mechanism of "involvement" of the Fas-Fas ligand pathway in MS. The right column on page 1609 of Elliot that is referred to by the Examiner, pertains to this second "involvement" of the Fas-Fas ligand pathway in MS, i.e. T cell elimination.

The present invention is drawn to a method of treating autoimmune demyelinating diseases with a Fas antagonist, which inhibits Fas-Fas ligand binding and suppresses apoptosis. Thus the present invention is based on the concept that the inhibition of Fas-Fas ligand pathway, i.e. inhibition of Fas-Fas ligand-induced apoptosis, is related to the treatment of autoimmune demyelinating diseases. With the second "involvement" of the Fas-Fas ligand pathway in MS, the inhibition of Fas-Fas ligand pathway would mean the destruction of the normal condition in a living body, i.e. in complete opposite from the invention. Thus, the present invention is far from obvious over the disclosure and discussion of this second involvement in Elliott.

Given the two mechanisms of involvement of the Fas-Fas ligand pathway in MS, which are in complete opposite to one another, i.e. a first mechanism of involvement which may lead to complications of the disease and a second mechanism of involvement that prevents the disease, and given the inconsistent data regarding the first mechanism of involvement, it would not be possible to predict by the one skilled in the art whether a

Fas antagonist would have a therapeutic effect on MS or not. It was not until the present invention has actually shown that the administration of Fas antagonist improves the condition of MS that the present invention could be suggested or achieved.

As the above remarks along with the amendments and remarks of December 31, 2002, entered on March 3, 2003, address and overcome the objections and rejections to the specification and claims, withdrawal of the objections and rejections and issuance of the Notice of Allowability are respectfully requested.

Should the Examiner have any questions regarding the present application, he is requested to please contact MaryAnne Armstrong, PhD (Reg. No. 40,069), in the Washington DC area, at (703) 205-8000.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

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GMM/MAA/
1110-0280P

Enclosures: Exhibits A and B

Exhibit A

Links

*134638

TUMOR NECROSIS FACTOR LIGAND SUPERFAMILY, MEMBER 6; TNFSF6

Alternative titles; symbols

FAS LIGAND; FASL
APOPTOSIS ANTIGEN LIGAND 1; APT1LG1
APOPTOSIS ANTIGEN LIGAND
CD95 LIGAND; CD95L
CD178 ANTIGEN; CD178

Gene map locus 1q23

TEXT

Life requires death. Elimination of unwanted cells is vital for embryogenesis, metamorphosis and tissue turnover, as well as for the development and function of the immune system. Mammalian development is tightly regulated not only by the proliferation and differentiation of cells but also by cell death. The cell death that occurs during development or tissue turnover is called programmed cell death, most of which proceeds via apoptosis. Apoptosis is morphologically distinguished from necrosis, which occurs during the accidental cell death caused by physical or chemical agents. During apoptosis, the cytoplasm of the affected cells condenses, and the nucleus also condenses and becomes fragmented. At the final stage of apoptosis, the cells themselves are fragmented (apoptotic bodies) and are phagocytosed by neighboring macrophages and granulocytes. Apoptosis occurs not only during programmed cell death, but also during the death process induced by some cytotoxic T cells. Suda et al. (1993) identified the ligand that triggers cell death by binding to the cell surface receptor variously known as FAS or APT1 (134637). This cell surface receptor was discovered in 1989 with the isolation of 2 monoclonal antibodies (anti-Fas and anti-Apo-1) that had the startling property of killing a human cell line used as the immunogen. Cell death occurred by apoptosis. Cloning of the genes revealed that the antigens recognized by the 2 monoclonal antibodies were one and the same. It is a transmembrane protein related to a family of receptors that includes the 2 tumor necrosis factor (TNF) receptors (191190, 191191). In mice, mutations at the lpr (lymphoproliferation) locus have a defect in the FAS antigen. The inability of homozygous mutant mice to mediate FAS-induced apoptosis provokes a complex immunologic disorder featuring defects in both the B and T lymphoid compartments. A very similar phenotype of mice homozygous for the gld (generalized lymphoproliferative disease) mutation suggested that the gld gene encodes the ligand for FAS. Suda et al. (1993) isolated the ligand from a cytotoxic T hybridoma by a sensitive expression cloning strategy. The amino acid sequence indicated that FAS ligand is a type II transmembrane protein that belongs to the tumor necrosis factor family. Northern hybridization revealed that the ligand is expressed in activated splenocytes and thymocytes, consistent with its involvement in T-cell-mediated cytotoxicity, and in several nonlymphoid tissues, such as testis. The FAS antigen is expressed not only in the cells of the immune system but also in the liver, lung, ovary, and heart, where its function is unclear.

Takahashi et al. (1994) isolated the murine Fasl gene and, by interspecific backcross analysis, localized it to the same region of mouse chromosome 1 as that occupied by the gld gene for 'generalized lymphoproliferative disease.' They showed that activated splenocytes from gld mice express Fasl mRNA. However, the Fas ligand protein in gld mice carried a point mutation in the C-terminal region, which is highly conserved among members of the TNF family. Recombinant gld Fas ligand expressed in COS cells could not induce apoptosis in cells expressing Fas.

Takahashi et al. (1994) isolated the chromosomal gene for human FasL. The human gene consists of approximately 8 kb and is split into 4 exons. The human FASL cDNA predicted a type II membrane protein consisting of 281 amino acids and a calculated M(r) of 31,759 that showed 76.9% amino acid sequence identity with the mouse protein. When expressed in COS cells, both human and mouse recombinant FasL induced apoptosis, indicating crossreactivity. A sequence of approximately 300 bp upstream of the ATG initiation codon was found to be highly conserved between mouse and human. Several transcription cis-regulatory elements such as SP-1, NF-kappa-B, and IRF-1 were recognized in this region. Takahashi et al. (1994) mapped the gene to 1q23 by fluorescence in situ hybridization.

Using GST pull-down analysis, Ghadimi et al. (2002) showed that the C-terminal SH3 domains of GRB2 (108355), FBP17 (606191), and PACSIN2 (604960), as well as other related proteins, bind to the polyproline-rich region of the cytoplasmic tail of FASL.

The pathogenesis of systemic lupus erythematosus (SLE; 152700) is multifactorial and polygenic. The apoptosis genes FAS and FASL are candidate contributory genes in SLE, as mutations of these genes result in autoimmunity in several murine models of SLE. In humans, FAS mutations result in autoimmune lymphoproliferative syndrome, or ALPS (e.g., 134637.0001). Wu et al. (1996) screened DNA from 75 patients with SLE by SSCP analysis for potential mutations of the extracellular domain of FASL. A heterozygous SSCP anomaly for FASL was identified in 1 SLE patient who exhibited lymphoadenopathy. Molecular cloning and sequencing indicated that the genomic DNA of this patient contained an 84-bp deletion within exon 4 of the FASL gene, resulting in a predicted 28-amino acid in-frame deletion (134638.0001). A study of peripheral blood mononuclear cells from this patient revealed decreased FASL activity, decreased activation-induced cell death, and increased T-cell proliferation after activation. Lenardo (1999) expressed the opinion that although this patient satisfied the rheumatologic criteria for a diagnosis of SLE, the features were more consistent with ALPS. This might be referred to as ALPS2 or ALPS1B, the form caused by mutations in the FAS gene being designated ALPS1A.

Viard et al. (1998) detected high levels of soluble FASL in the sera of patients with toxic epidermal necrolysis (TEN). Keratinocytes of TEN patients produced FASL, which induced keratinic apoptosis. Incubating keratinocytes with intravenous immunoglobulin (IVIG) completely inhibited FAS-mediated keratinocyte apoptosis. A naturally occurring anti-FAS immunoglobulin present in IVIG blocks the FAS receptor and mediates this response. Ten patients with TEN were treated with IVIG. Progression of skin disease was rapidly reversed in all cases.

Hahne et al. (1996) stated that, despite the existence of melanoma-specific cytolytic T cells in tumor-infiltrating lymphocytes and in peripheral blood from melanoma patients, and the definition of 12 CTL-defined melanoma peptide antigens, melanoma cells are able to avoid immune detection in most instances. The investigators proposed that FASL-expressing melanoma cells may kill FAS-sensitive activating T lymphocytes. They analyzed FASL expression in melanoma cells and demonstrated substantial quantities of FASL in lysates of a series of human melanoma cells. Two molecular species were identified: a 40-kD membrane-bound FASL and a 27-kD extracellular FASL. Hahne et al. (1996) also demonstrated that the majority of cells infiltrating the tumors were FAS-positive. No FASL was found in normal melanocytes of the skin, suggesting that FASL upregulation occurs during tumorigenesis. Hahne et al. (1996) proposed that FASL-expressing melanoma cells might induce apoptosis of FAS-sensitive tumor infiltrating cells. They reported that injection of FasL+ mouse melanoma cells in mice led to rapid tumor formation. When FasL+ mouse melanoma cells were injected

into FAS-deficient mutant mice, tumorigenesis was delayed. These findings led Hahne et al. (1996) to conclude that FASL may contribute to the immune privilege of tumors. They proposed further that pharmacologic products that render infiltrating T cells insensitive to FASL-induced killing may break the immunologic unresponsiveness to melanoma and provide a complementary approach in the therapy of malignant melanoma.

DNA-damaged cells can either repair the DNA or be eliminated through a homeostatic control mechanism mediated by p53 (191170) termed 'cellular proofreading.' Elimination of DNA-damaged cells after UV radiation through sunburn cell (or apoptotic keratinocyte) formation is thought to be pivotal for the removal of precancerous skin cells. Hill et al. (1999) demonstrated that sunburn cell formation is dependent upon FasL. Chronic exposure to UV radiation caused 14 of 20, or 70%, of FasL-deficient mice and 1 of 20, or 5%, of wildtype mice to accumulate p53 mutations in the epidermis. Hill et al. (1999) concluded that FASL-mediated apoptosis is important for skin homeostasis, suggesting that the dysregulation of FAS-FASL interactions may be central to the development of skin cancer.

In the United States more than 43,000 corneal transplants are performed each year, making it the most common form of solid tissue transplantation, and second only to bone marrow transplants in overall numbers performed. Corneal transplantation is also one of the most successful types of transplantation with failure rates at only 10 to 15% after 1 year and approximately 30% after 5 years. Stuart et al. (1997) demonstrated that the very high percentage of successful corneal transplants, without tissue matching or immunosuppressant therapy, is related to the expression of abundant functional FASL in the cornea, capable of killing FASL(+) lymphoid cells. Using a mouse model for corneal allograft transplantation, FasL (+) orthografts were accepted at a rate of 45%, whereas FasL(-) or normal grafts transplanted to Fas(-) mice were rejected 100% of the time.

Pestano et al. (1999) identified a differentiative pathway taken by CD8 cells bearing receptors that cannot engage class I MHC (see 142800) self-peptide molecules because of incorrect thymic selection, defects in peripheral MHC class I expression, or antigen presentation. In any of these cases, failed CD8 T-cell receptor coengagement results in downregulation of genes that account for specialized cytolytic T-lymphocyte function and resistance to cell death (CD8-alpha/beta, see 186730; granzyme B, 123910; and LKLF, 602016), and upregulation of Fas and FasL death genes. Thus, MHC engagement is required to inhibit expression and delivery of a death program rather than to supply a putative trophic factor for T cell survival. Pestano et al. (1999) hypothesized that defects in delivery of the death signal to these cells underlie the explosive growth and accumulation of double-negative T cells in animals bearing Fas and FasL mutations, in patients that carry inherited mutations of these genes, and in about 25% of systemic lupus erythematosus patients that display the cellular signature of defects in this mechanism of quality control of CD8 cells.

Grassme et al. (2000) showed that Pseudomonas aeruginosa infection induces apoptosis of lung epithelial cells by activation of the endogenous CD95/CD95L system. Deficiency of CD95 or CD95L on epithelial cells prevented apoptosis of lung epithelial cells in vivo as well as in vitro. The importance of CD95/CD95L-mediated lung epithelial cell apoptosis was demonstrated by the rapid development of sepsis in mice deficient in either CD95 or CD95L, but not in normal mice, after P. aeruginosa infection.

Testis is a remarkably immune-privileged site, long known for its ability to support allogeneic and xenogeneic tissue transplants. Bellgrau et al. (1995) reported results suggesting that expression of FasL by Sertoli cells accounts for the immune-privileged nature of testis. Testis grafts derived from mice that can express functional FasL survived indefinitely when transplanted under the kidney capsule of allogeneic mice, whereas testis graft derived from mutant gld mice, which express nonfunctional ligand, were rejected. The authors speculated that FasL expression in the testis probably acts by inducing apoptotic cell death of Fas-expressing, recipient T cells activated in response to graft antigens. D'Alessio et al. (2001) demonstrated that the attribution of testicular expression of FasL to Sertoli cells

is erroneous and that FasL transcription instead occurs in meiotic and postmeiotic germ cells, whereas the protein is only displayed on mature spermatozoa. These findings point to a significant role of the Fas system in the biology of mammalian reproduction.

Cytomegalovirus (CMV) is a persistent viral pathogen that resides in monocyte/macrophages and dendritic cells (DCs), critical antigen-presenting cells in the immune system. In fetal and compromised immune systems, CMV can be fatal. Raftery et al. (2001) found that recent CMV isolates, but not fibroblast-adapted CMV strains, could infect mature DCs with no change in some cell surface markers. On the other hand, flow cytometric analysis indicated a slight upregulation of the costimulatory molecules CD40 (TNFRSF5; 109535), CD80 (112203), and CD86 (601020), as well as a downregulation of MHC class I and class II molecules. Functional analysis showed that CMV-infected mature DCs suppress T-cell proliferation. Further FACS analysis demonstrated an upregulation of TRAIL (603598) and FASL, molecules that induce T-cell apoptosis through caspase (see CASP8; 601763)-dependent mechanisms, on DCs. Raftery et al. (2001) concluded that CMV evades the immune response by first downregulating MHC antigens, thereby diminishing T-cell responses, followed by an upregulation of apoptosis-inducing ligands that delete activated T cells. They also proposed that nondeletional, possibly cytokine-mediated mechanisms are involved in T-cell suppression.

Mice instilled with silica develop severe pulmonary inflammation with local production of TNFA and interstitial neutrophil and macrophage infiltration in the lungs, a phenotype that resembles silicosis, an industrial era disease that afflicts certain mining professions. Borges et al. (2001) found that Fasl-deficient gld mice had reduced neutrophil extravasation into the bronchoalveolar space, did not show TNFA production increases, and did not have pulmonary inflammation in response to silica. Silica induced deferoxamine-inhibitable Fasl expression in wildtype lung macrophages in vivo and in vitro, as well as apoptosis of pulmonary macrophages. Analysis of bone marrow chimeras and local adoptive transfer experiments demonstrated that wildtype but not Fasl-deficient lung macrophages recruited neutrophils and initiated silicosis. The induction of silicosis could be blocked by the administration of neutralizing anti-Fasl antibodies. Borges et al. (2001) proposed that apoptotic cell death is required for neutrophil extravasation and pulmonary inflammation.

Natural inhibitors of angiogenesis are able to block pathologic neovascularization without harming the preexisting vasculature. Volpert et al. (2002) demonstrated that 2 such inhibitors, thrombospondin I (188060) and pigment epithelium-derived factor (172860), derive specificity for remodeling vessels from their dependence on Fas/FasL-mediated apoptosis to block angiogenesis. Both inhibitors upregulated FasL on endothelial cells. Expression of the essential partner of FasL, Fas receptor, was low on quiescent endothelial cells and vessels but greatly enhanced by inducers of angiogenesis, thereby specifically sensitizing the stimulated cells to apoptosis by inhibitor-generated FasL. The antiangiogenic activity of thrombospondin I and pigment epithelium-derived factor both in vitro and in vivo was dependent on this dual induction of Fas and FasL and the resulting apoptosis. Volpert et al. (2002) concluded that this example of cooperation between pro- and antiangiogenic factors in the inhibition of angiogenesis provides one explanation for the ability of inhibitors to select remodeling capillaries for destruction.

ALLELIC VARIANTS
(selected examples)

.0001 SYSTEMIC LUPUS ERYTHEMATOSUS, SUSCEPTIBILITY TO [TNFSF6, 84-BP DEL, EX4]

AUTOIMMUNE LYMPHOPROLIFERATIVE SYNDROME TYPE IB

In a patient with SLE (152700) who exhibited lymphadenopathy, Wu et al. (1996) identified an 84-bp

deletion within exon 4 of the FASL gene, resulting in a predicted 28-amino acid in-frame deletion.

As stated earlier, Lenardo (1999) suggested that this patient should be classified as an instance of autoimmune lymphoproliferative syndrome (601859) due to mutation in the FASL gene. This form of ALPS has been designated ALPS1B, the form due to mutation in the FAS gene being ALPS1A.

REFERENCES

1. Bellgrau, D.; Gold, D.; Selawry, H.; Moore, J.; Franzusoff, A.; Duke, R. C.:
A role for CD95 ligand in preventing graft rejection. *Nature* 377: 630-632, 1995.
PubMed ID : 7566174

2. Borges, V. M.; Falcao, H.; Leite-Junior, J. H.; Alvim, L.; Teixeira, G. P.; Russo, M.; Nobrega, A. F.; Lopes, M. F.; Rocco, P. M.; Davidson, W. F.; Linden, R.; Yagita, H.; Zin, W. A.; DosReis, G. A.:
Fas ligand triggers pulmonary silicosis. *J. Exp. Med.* 194: 155-163, 2001.
PubMed ID : 11457890

3. D'Alessio, A.; Riccioli, A.; Lauretti, P.; Padula, F.; Muciaccia, B.; De Cesaris, P.; Filippini, A.; Nagata, S.; Ziparo, E.:
Testicular FasL is expressed by sperm cells. *Proc. Nat. Acad. Sci.* 98: 3316-3321, 2001.
PubMed ID : 11248076

4. Ghadimi, M. P.; Sanzenbacher, R.; Thiede, B.; Wenzel, J.; Jing, Q.; Plomann, M.; Borkhardt, A.; Kabelitz, D.; Janssen, O.:
Identification of interaction partners of the cytosolic polyproline region of CD95 ligand (CD178). *FEBS Lett.* 519: 50-58, 2002.
PubMed ID : 12023017

5. Grassme, H.; Kirschnek, S.; Riethmueller, J.; Riehle, A.; von Kurthy, G.; Lang, F.; Weller, M.; Gulbins, E.:
CD95/CD95 ligand interactions on epithelial cells in host defense to Pseudomonas aeruginosa. *Science* 290: 527-530, 2000.
PubMed ID : 11039936

6. Hahne, M.; Rimoldi, D.; Schroter, M.; Romero, P.; Schreier, M.; French, L. E.; Schneider, P.; Bornand, T.; Fontana, A.; Lienard, D.; Cerottini, J. C.; Tschopp, J.:
Melanoma cell expression of Fas (Apo-1/CD95) ligand: implications for tumor immune escape. *Science* 274: 1363-1366, 1996.
PubMed ID : 8910274

7. Hill, L. L.; Ouhtit, A.; Loughlin, S. M.; Kripke, M. L.; Ananthaswamy, H. N.; Owen-Schaub, L. B.:
Fas ligand: a sensor for DNA damage critical in skin cancer etiology. *Science* 285: 898-900, 1999.
PubMed ID : 10436160

8. Lenardo, M. J.:
Personal Communication. Bethesda, Md., 1/14/1999.

9. Pestano, G. A.; Zhou, Y.; Trimble, L. A.; Daley, J.; Weber, G. F.; Cantor, H.:
Inactivation of misselected CD8 T cells by CD8 gene methylation and cell death. *Science* 284: 1187-1191, 1999.
PubMed ID : 10325233

10. Raftery, M. J.; Schwab, M.; Eibert, S. M.; Samstag, Y.; Walczak, H.; Schonrich, G.:
Targeting the function of mature dendritic cells by human cytomegalovirus: a multilayered viral

defense strategy. *Immunity* 15: 997-1009, 2001.
PubMed ID : 11754820

11. Stuart, P. M.; Griffith, T. S.; Usui, N.; Pepose, J.; Yu, X.; Ferguson, T. A. :
CD95 ligand (FasL)-induced apoptosis is necessary for corneal allograft survival. *J. Clin. Invest.* 99: 396-402, 1997.
PubMed ID : 9022072

12. Suda, T.; Takahashi, T.; Golstein, P.; Nagata, S. :
Molecular cloning and expression of the Fas ligand, a novel member of the tumor necrosis factor family. *Cell* 75: 1169-1178, 1993.
PubMed ID : 7505205

13. Takahashi, T.; Tanaka, M.; Brannan, C. I.; Jenkins, N. A.; Copeland, N. G.; Suda, T.; Nagata, S. :
Generalized lymphoproliferative disease in mice, caused by a point mutation in the Fas ligand. *Cell* 76: 969-976, 1994.
PubMed ID : 7511063

14. Takahashi, T.; Tanaka, M.; Inazawa, J.; Abe, T.; Suda, T.; Nagata, S. :
Human Fas ligand: gene structure, chromosomal location and species specificity. *Int. Immun.* 6: 1567-1574, 1994.
PubMed ID : 7826947

15. Viard, I.; Wehrli, P.; Bullani, R.; Schneider, P.; Holler, N.; Salomon, D.; Hunziker, T.; Saurat, J.-H.; Tschopp, J.; French, L. E. :
Inhibition of toxic epidermal necrolysis by blockade of CD95 with human intravenous immunoglobulin. *Science* 282: 490-493, 1998.
PubMed ID : 9774279

16. Volpert, O. V.; Zaichuk, T.; Zhou, W.; Reiher, F.; Ferguson, T. A.; Stuart, P. M.; Amin, M.; Bouck, N. P. :
Inducer-stimulated Fas targets activated endothelium for destruction by anti-angiogenic thrombospondin-1 and pigment epithelium-derived factor. *Nature Med.* 8: 349-357, 2002.
PubMed ID : 11927940

17. Wu, J.; Wilson, J.; He, J.; Xiang, L.; Schur, P. H.; Mountz, J. D. :
Fas ligand mutation in a patient with systemic lupus erythematosus and lymphoproliferative disease. *J. Clin. Invest.* 98: 1107-1113, 1996.
PubMed ID : 8787672

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mgross : 10/30/2000
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alopez : 8/5/1999
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mark : 6/14/1997
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terry : 11/26/1996
mark : 10/17/1996
mark : 10/9/1996
mark : 12/13/1995
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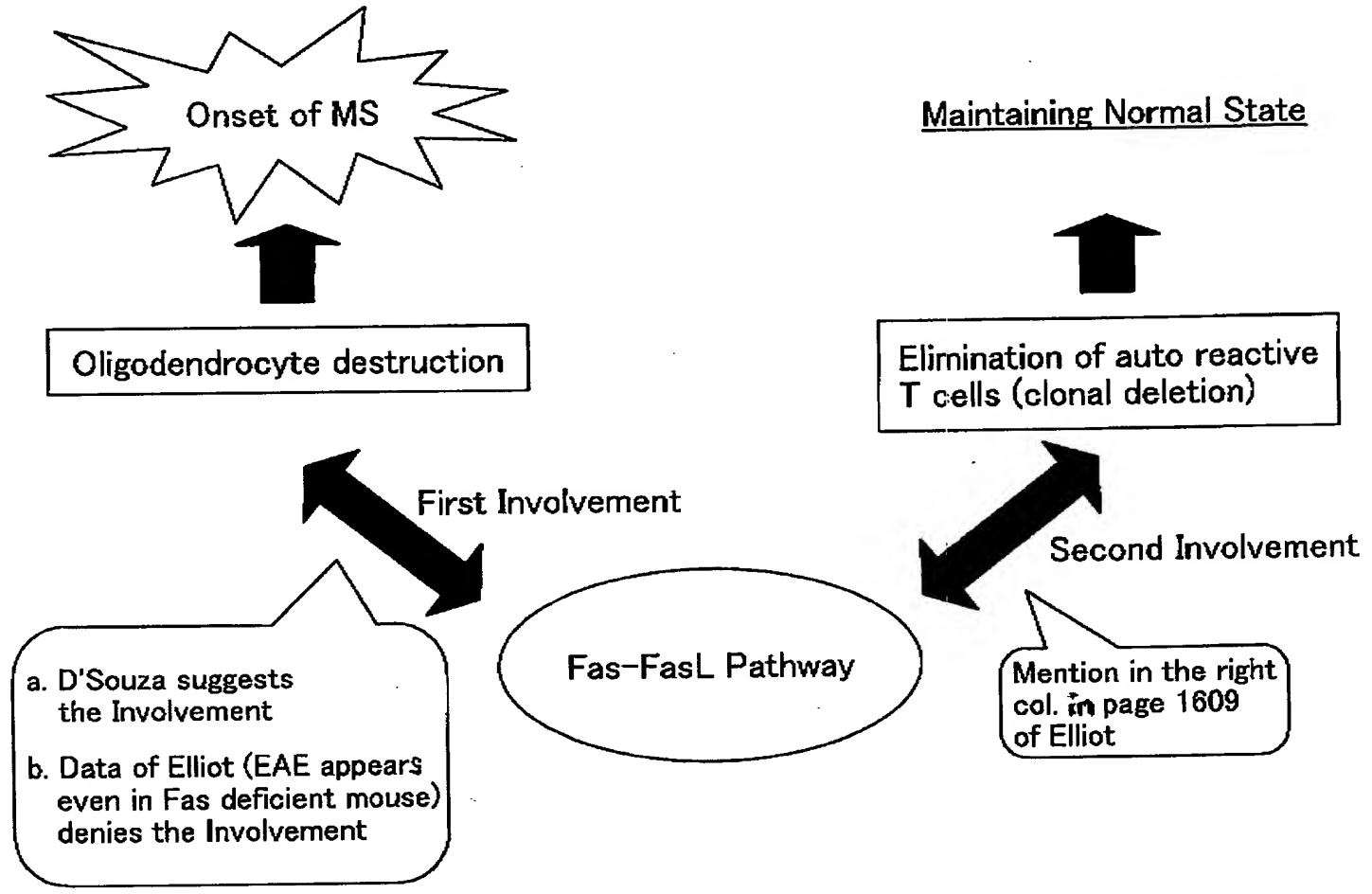
Exhibit B


Onset of MS
Maintaining Normal State
Oligodendrocyte destruction
Elimination of auto reactive T cells (clonal deletion)
First Involvement
Second Involvement
a. D'Souza suggests the Involvement
b. Data of Elliot (EAE appears even in Fas deficient mouse) denies the Involvement
Fas-FasL Pathway
Mention in the right col. in page 1609 of Elliot